Risk of Colorectal Adenoma and Carcinoma After Colectomy for Colorectal Cancer in Patients Meeting Amsterdam Criteria

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Objective: To report the risk of metachronous colorectal neoplasia after colectomy for cancer in Hereditary Nonpolyposis Colorectal Cancer (HNPCC) syndrome.

Summary background data: Patients meeting Amsterdam criteria for diagnosis of HNPCC have a lifetime colorectal cancer risk approaching 80%, and a metachronous cancer rate of approximately 25%. Therefore, when colon cancer is diagnosed, total rather than segmental colectomy is advocated. However, information about adenoma and carcinoma risk after index surgery is still underreported.

Methods: A hereditary colorectal cancer database was reviewed for patients meeting Amsterdam criteria who underwent colectomy for cancer. Patient demographics, surgical management, and results of follow-up were recorded. Metachronous colorectal adenoma and carcinoma development were the primary end points.

Results: A total of 296 patients (253 with segmental colectomy and 43 with total colectomy/ileorectal anastomosis) were analyzed. Of the 253 segmental colectomy patients, 221 (88%) had postoperative endoscopic surveillance with median follow-up of 104 months. In 74 patients (33%), 256 adenomas were detected, including 140 high-risk adenomas in 48 patients (22%). Fifty-five patients (25%) developed a second colorectal cancer at a median of 69 months after index surgery. Stages of the metachronous cancers were I-16, II-18, III-12, and IV-2. By comparison, 4 of 38 patients (11%) who underwent total colectomy developed subsequent high-risk adenomas and 3 (8%) developed metachronous cancer.

Conclusions: Amsterdam patients undergoing partial colectomy have a high rate of metachronous high-risk adenomas and carcinomas. Total colectomy for the index cancer is the procedure of choice. For either surgical option, yearly endoscopic surveillance is essential to remove premalignant adenomas.

(*Ann Surg* 2010;252: 507–513)

With approximately 140,000 new diagnoses annually, colorectal cancer is the third most common cancer in the United States.[1] Most colorectal cancers are sporadic and occur secondary to environmental factors with some contribution from weak familial effects. However, approximately 5% of colorectal cancers occur in the setting of a heritable syndrome, in which germline mutations of a tumor suppressor gene or a DNA repair gene confer a high risk of colorectal and extracolonic cancer development at a young age. The most common of these hereditary colorectal cancer syndromes is Lynch syndrome, a form of Hereditary Nonpolyposis Colorectal Cancer (HNPCC) caused by an inactivating mutation in 1 of 4 DNA mismatch repair genes.[2] Affected families have a "mutator phenotype," where uncorrected DNA mismatches create multiple mutations throughout the genome. This is clinically evident as a 6-fold increase in risk of colorectal cancer,[3] a synchronous cancer rate of 18%, and a metachronous cancer rate of 16% to 24%.[4,5] Because the germline mutations in mismatch repair genes are dominantly inherited, there is usually a strong family history of colorectal and other cancers occurring at a young age. This family history has been used as a tool to categorize high-risk families and to select families for genetic testing.

Formal family history criteria were first defined in 1991 as tools to standardize the syndrome for research purposes, but these criteria have since become used clinically for diagnosis. These became known as the Amsterdam Criteria.[6] The original (Amsterdam I) criteria were revised in 1999 (Amsterdam II) to correct for insensitivity because of omission of extracolonic cancers from the original criteria.[7] More recently, a further modification of the Amsterdam criteria (Amsterdam-like) allowed for the inclusion of high-risk adenomas as a surrogate for 1 cancer to correct for the phenotype attenuation that has accompanied increasing use of colonoscopic surveillance and polypectomy.

Because the risk of developing colorectal cancer approaches nearly 80% by age 50 for patients with HNPCC, annual screening by colonoscopy is recommended beginning at age 25.[8–10] Surgery is generally reserved for patients who develop endoscopically unmanageable polyps or adenocarcinomas, although prophylactic colectomy is sometimes performed. The options for surgical management of a colon cancer in a patient with HNPCC are either a standard segmental colectomy as would be done for a sporadic cancer in the same location, or a total colectomy with ileorectal anastomosis. This more extensive resection is partially prophylactic, and aims to reduce the risk of metachronous cancer. Although both clinical evidence and expert opinion support the routine use of extended resection,[11–13] this is not general practice for several reasons. First, not all patients are correctly diagnosed with HNPCC at the time of surgery and therefore the high risk of metachronous cancer is not appreciated. Second, patients may be diagnosed but choose not to undergo a more extensive operation. Third, patients who are elderly or have comorbidities with low life expectancy or who have poor anal muscle tone may be better served by a more limited operation that also preserves more colon for better function. Whatever the reason influencing choice of surgery, it is important to understand the expectations and future risk associated with either option.

The risk of patients with HNPCC developing metachronous colorectal cancer after segmental resection has been reported between 16% and 26%.[4,5,12] However, the data regarding the natural history of patients undergoing segmental colectomy are sparse and has been reported in relatively small patient populations. In particular, data describing the results of colonoscopic surveillance after

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Presented at the 130th Annual Meeting of the American Surgical Association; April 8, 2010; Chicago, IL.

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ISSN: 0003-4932/10/25203-0507
DOI: 10.1097/SLA.0b013e3181f20bd2

segmental colectomy in HNPCC and its efficacy in removing metachronous adenomas are few. This study reports a large population of patients from Amsterdam Criteria-positive families who underwent an index colectomy, and defines subsequent adenoma burden and risk of metachronous cancers depending on the extent of surgery performed.

METHODS

A single institution hereditary colorectal cancer database (Cologene© pedigree and clinical data management software, available at: http://colorectal.ccf.org/cologene) was used to collect and retrieve family data. The database was reviewed for patients within families meeting Amsterdam I, II, or like criteria, who underwent surgery for colorectal cancer. Patients in the Registry receiving treatment between the years 1950 and 2009 were included. Patients with rectal cancer as the index cancer were not included in the query and those treated by proctocolectomy were excluded. Patients presenting with stage IV disease were not included in the follow-up data.

Amsterdam criteria for a family were defined as follows:

Amsterdam I: Three or more family members diagnosed with colorectal cancer, 1 of whom is a first-degree relative of the other 2; 2 successive generations are affected; 1 or more of the cancers is diagnosed before age 50 years; familial adenomatous polyposis is excluded.

Amsterdam II: Three or more family members diagnosed with an HNPCC-related cancer (colorectum, endometrium, ovary, stomach, small intestine, hepatobiliary, renal pelvis, or ureter), 1 of whom is a first-degree relative of the other 2; 2 successive generations are affected; 1 or more of the HNPCC-related cancers is diagnosed before age 50 years; familial adenomatous polyposis is excluded.

Amsterdam-like: Three or more family members diagnosed with an HNPCC-related cancer (colorectum, endometrium, ovary, stomach, small intestine, hepatobiliary, renal pelvis, or ureter), 1 of the 3 family members may have an advanced adenoma (any adenoma ≥1 cm diameter, any size adenoma with high-grade dysplasia or ≥25% villous architecture, 3 or more adenomas of any size or histology); 1 of whom is a first-degree relative of the other 2; 2 successive generations are affected; 1 or more of the HNPCC-related cancers is diagnosed before age 50 years; familial adenomatous polyposis has been excluded.

Cologene database software and/or patient charts were reviewed to record the clinical criteria for inclusion, patient demographics, type of surgery performed, tumor characteristics, and subsequent follow-up. Germline mutations in the mismatch repair genes *MLH1, MSH2, MSH6,* or *PMS2* were recorded for patients who had undergone genetic testing. The primary study end points were postoperative adenoma formation and development of a metachronous cancer in the colon or rectum. High-risk adenomas are defined as above in Amsterdam-like criteria. For anatomic classification, colon proximal to and including the splenic flexure was considered right colon. A subtotal colectomy with an ileosigmoid anastomosis was considered equivalent to a total colectomy and ileorectal anastomosis for this study since the majority of colon is removed and the surveillance approach is the same. Both rectum and sigmoid surveillance may be accomplished by flexible sigmoidoscopy as an office procedure without sedation or mechanical bowel preparation.

TABLE 1. Patient Population Demographics and Tumor Characteristics

	Total Population N = 296	Segmental Colectomy N = 253	Total Colectomy N = 43
Gender			
Male	143 (48%)	115 (45%)	28 (65%)
Female	153 (52%)	138 (55%)	15 (35%)
Age at index surgery, mean ± SD	52 ± 14	53 ± 14	47 ± 14
Clinical criteria			
Amsterdam 1	211	182	29
Amsterdam 2	14	10	4
Amsterdam-like	71	61	10
Index cancer location			
Right	148	125	23
Left	140	123	17
Both	8	5	3
Index cancer stage*			
I	63 (25%)	52 (25%)	11 (28%)
II	81 (33%)	71 (34%)	10 (26%)
III	72 (29%)	60 (29%)	12 (31%)
IV	33 (13%)	27 (13%)	6 (15%)

*Cancer stage was unknown for 47 patients.
SD indicates standard deviation.

RESULTS

Patient and Cancer Characteristics

There were 311 patients whose families met 1 of the 3 Amsterdam criteria. Fifteen patients who underwent total proctocolectomy were excluded. Thus, 296 patients who were treated and followed between the years 1950 and 2009 were analyzed. Seventy-four patients (25%) underwent their initial surgery at Cleveland Clinic, whereas 222 (75%) underwent index surgery elsewhere and then were referred to the David B. Jagelman Inherited Colorectal Cancer Registries at the Cleveland Clinic. Patient demographics, clinical criteria, and cancer characteristics are listed in Table 1. Sixteen patients had genetic testing and 11 (69%) were found to have germline mutations in the mismatch repair genes *MLH1* (N = 5), *MSH2* (N = 5), and *MSH6* (N = 1). Because this represented a small proportion of the study population, this group was not analyzed separately.

Surgical Treatment

In all, 253 patients (85%) underwent a segmental colectomy as index procedure and 43 patients (15%) underwent a total or subtotal colectomy with ileorectal or ileosigmoid anastomosis. A segmental colectomy was defined as any colectomy less than a total colectomy with an ileorectal anastomosis or a subtotal colectomy with an ileosigmoid anastomosis. Of the 74 patients who were initially treated at the Cleveland Clinic, 26 (35%) underwent a total colectomy. Of the 222 patients who were initially treated elsewhere, 17 (8%) underwent a total colectomy.

Follow-up Colonoscopy and Metachronous Adenoma Risk

Segmental Resection

Of the 253 patients who underwent a segmental colectomy, 221 (87%) had documented follow-up endoscopy. The median follow-up was 104 months (interquartile range: 193 months). The

TABLE 2. Metachronous Adenoma Formation

	Total Population N = 296	Segmental Colectomy N = 253	Total Colectomy N = 43
Patients with endoscopic surveillance	254 (87%)	221 (87%)	38 (88%)
Median follow-up, mo (IQR)	104 (195)	104 (193)	104 (217)
Mean endoscopies per yr (SD)	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.3
Median interval between endoscopies, mo (range)	17 (12–204)	21 (12–102)	17 (12–204)
Patients with adenomas (%)*	78 (31%)	74 (33%)	4 (11%)
Total no. adenomas	269	256	13
Patients with high-risk adenomas (%)	52 (20%)	48 (22%)	4 (11%)
Total no. high-risk adenomas	146	140	6
Types of high-risk adenomas			
≥10 mm	54	50	4
High-grade dysplasia	16	15	1
Villous histology	56	53	3
≥3 adenomas at single exam	16	16	0
Median time from previous endoscopy to identification of high-risk adenoma, mo (IQR)	15 (37)	13 (38)	35 (15)

*Percentages are based on number of patients with documented endoscopic follow-up; patients with stage IV cancer excluded from follow-up.
IQR indicates interquartile range; SD, standard deviation.

TABLE 3. Metachronous Adenocarcinoma Formation

	Total Population N = 296	Segmental Colectomy N = 253	Total Colectomy N = 43
Median follow-up (IQR)	104 (195)	104 (193)	104 (217)
Patients with endoscopic surveillance	254 (87%)	221 (87%)	38 (88%)
Patients with metachronous cancer (%)*	58 (23%)	55 (25%)	3 (8%)
Mean endoscopies per yr (SD)	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.3
Median time from index surgery to second cancer, mo (IQR)	76 (172)	69 (162)	227 (59)
Median time from previous endoscopy to identification of cancer, mo (IQR)	—	18 (33)	†
Metachronous cancer stage			
I	18	16	2
II	18	18	0
III	14	12	1
IV	2	2	0
Unknown	7	7	0

*Percentages are based on number of patients with documented endoscopic follow-up.
†The intervals for the 3 patients were 220, 227, and 318 months.
IQR indicates interquartile range; SD, standard deviation.

mean number of endoscopies was 0.7 ± 0.3 per year. The mean interval between colonoscopies was 25 ± 22 months.

Of 221 patients, 101 (46%) underwent subsequent polypectomy. A total of 256 adenomas were removed from 74 patients (33%). Of these adenomas, 140 were high-risk, developing in 48 patients (22%). The median number of colonoscopies per patient was 0.6 per year. The mean time from previous colonoscopy to detection of a high-risk adenoma was 35 ± 59 months (median, 13 months; interquartile range, 38 months). Twenty-six patients had multiple high-risk adenomas either at the same examination or at subsequent evaluations. The types of high-risk adenomas are shown in Table 2. In addition to adenomas, 163 hyperplastic polyps and 127 sessile serrated polyps were removed in this population.

Subtotal or Total Colectomy

Of the 43 patients who underwent a subtotal or total colectomy, 38 (88%) had documented follow-up endoscopy. The median follow-up was 104 months (interquartile range, 217 months). The mean number of endoscopies was 0.6 ± 0.3 per year. The mean interval between endoscopies was 26 ± 18 months. Of 38 patients, 10 (26%) underwent polypectomy. A total of 11 adenomas were removed from 4 patients (11%). Of these adenomas, 6 were high-risk adenomas, developing in 4 patients (11%). The mean time from previous proctosigmoidoscopy to detection of high-risk adenoma was 32 ± 12 months. The types of high-risk adenomas are shown in Table 2. In addition to the adenomas, 14 hyperplastic polyps and 9 sessile serrated polyps were removed from these patients.

Metachronous Colorectal Cancer Risk

Segmental Resection

Of the 253 patients who underwent a segmental colectomy, 221 (87%) had documented follow-up at a median follow-up of 104 months (interquartile range, 193 months). Of the 221, 55 (25%) developed a metachronous colorectal cancer. The median number of colonoscopies per patient was 0.3 per year. The mean time from index cancer to development of the second cancer was 115 ± 118 months (median: 69 months, interquartile range: 162 months). There were 16 Stage I cancers, 18 Stage II, 12 Stage III, and 2 Stage IV cancers. The stages for 7 metachronous cancers were unknown. The median time from previous colonoscopy to detection of cancer was 34 months (range: 7–90 months). These data are summarized in Table 3. Four interval cancers were detected within 12 months of the previous colonoscopy. All 4 of these cancers were early stage cancers (2 stage I and 2 stage II). Of the 55 patients who developed a second cancer, 26 patients had 59 adenomas, including 49 high-risk adenomas in 21 patients. Twenty-nine patients did not have precursor lesions detected before developing a second cancer. The high-risk adenomas are described in Table 4.

Subtotal or Total Colectomy

Of the 43 patients who underwent a total colectomy, 38 (88%) had documented follow-up at a median of 104 months (interquartile range, 217 months). Of the 38 patients, 3 (8%) developed a metachronous rectal cancer. The intervals from index cancer to development of the second cancer were 200, 227, and 318 months. There were 2 stage I cancers and 1 stage III cancer. The intervals between the previous proctosigmoidoscopy and the examination that detected the second cancers were 41, 45, and 90 months. These data are summarized in Table 3. Three adenomas had been removed from 2 of the 3 patients who developed a second cancer. Two of these adenomas were high-risk adenomas.

Summary of Metachronous High-Risk Adenomas or Carcinomas

Of the 221 patients followed after segmental colectomy, 48 had metachronous high-risk adenomas, 55 had metachronous can-

TABLE 4. Adenomas Removed From Patients That Developed Metachronous Cancer

	Total Population	Segmental Colectomy	Total Colectomy
Patients with metachronous cancer (%)*	58 (23%)	55 (25%)	3 (8%)
Patients without detected precursor adenomas (%)	30	29	1
Patients with interval adenoma removal (%)†	28 (48%)	26 (47%)	2 (67%)
Total no. adenomas	62	59	3
Patients with high-risk adenomas (%)†	23 (40%)	21 (38%)	2 (67%)
Total no. high-risk adenomas	51	49	2
Types of high-risk adenomas			
≥10 mm	20	18	2
High-grade dysplasia	14	13	1
Villous histology	13	13	0
≥3 adenomas at single exam	6	6	0

*Percentages are based on number of patients with documented endoscopic follow-up.
†Percentages are based on number of patients with a metachronous colorectal cancer.

cer, and 21 had both. Thus, 82 patients (37%) developed either metachronous high-risk adenomas or cancer. By comparison, of the 38 patients followed after total colectomy, 4 had metachronous high-risk adenomas, 3 had metachronous cancer, and 2 had both. Thus, 5 (13%) had either high-risk adenomas or cancer.

DISCUSSION

Although total abdominal colectomy is recommended for patients with HNPCC, this study shows that historically most patients have been treated by segmental colectomy either because of a deliberate choice or failure to diagnosis the syndrome and appreciate the risk. Defining the risk for neoplasia in the remaining colorectal epithelium after index cancer surgery in HNPCC is essential. This study reports a high rate of adenoma and adenocarcinoma formation after segmental colectomy and supports the use of total colectomy to treat colon cancer associated with HNPCC. The results also emphasize the fact that substantial neoplasia risk is present even after colectomy and ileorectal anastomosis, and that even these patients need careful, regular surveillance.

Surveillance colonoscopy is the preferred method of colorectal cancer prevention in patients with HNPCC, even though interval cancers may occur when colonoscopies are more than a year apart[14,15] and 4 interval cancers in our study developed within 1 year surveillance. In our study, patients who developed metachronous cancer had a longer median interval between colonoscopies, approximately 3 years, compared with those who had adenomas or high-risk adenomas removed, 1.4 and 1.8 years, respectively. These data suggest that shorter screening intervals detect precancerous adenomas before cancer develops. Colonoscopic surveillance in HNPCC has been shown to be effective in reducing the rate of colorectal cancer formation by 63%, allows cancer detection at an earlier stage, and minimizes mortality from cancer.[14] Detection of high-risk adenomas in 20% our total population confirms the importance of polypectomy in cancer prevention, and underlines the importance of the Amsterdam-like criteria in optimizing the sensitivity of family history in identifying HNPCC. Furthermore, HNPCC patients with advanced adenomas, without timely colonoscopy and polypectomy, would likely develop cancer as the natural progression from high-risk adenomas. Timely surveillance is even more important given an accelerated adenoma-to-carcinoma sequence in HNPCC[16–18] and also a reported missed adenoma rate of up to 55% using conventional colonoscopy.[19]

In addition to adenomas, a large number of non-neoplastic polyps were removed. The most common histologic diagnoses were hyperplastic polyps and sessile serrated polyps, both of which have been shown to have malignant potential through the serrated pathway of colorectal oncogenesis[20] and also have been associated with HNPCC.[21,22] Even if a small proportion of these lesions progress to cancer, polypectomy would reduce the rate of colorectal cancer formation in these patients. Thus, the number of patients in our study whose cancer risk was decreased by polypectomy may be underestimated by not including serrated lesions as study endpoints.

The rates of metachronous cancer development in this study, 25% after segmental colectomy and 8% after total colectomy, are consistent with other reports in the literature.[12,23,24] The literature reflects variable approaches to colonoscopic surveillance. The Cleveland Clinic data, previously reported by Van Dalen et al, show a low rate of metachronous cancers in a group of patients who underwent a relatively rigid program of postoperative colonoscopy.[23] This suggests that segmental colectomy followed by yearly colonoscopy may be as effective as total colectomy in minimizing metachronous cancer. Such an approach however, relies on careful and accurate colonoscopy in totally compliant patients. However, even with strict adherence, interval cancers still occur, and may happen more often as patient's age and the colorectal epithelium becomes more unstable under an increasing burden of mutations. In this study, more than 90% of patients with second cancers had been cared for outside of the Cleveland Clinic, and outside the setting of a specialized registry for patients with hereditary colorectal cancer.

One of the main concerns affecting the decision for segmental rather than total colectomy in patients with an HNPCC-associated colon cancer is the likely decreased bowel function postoperatively and its effect on quality of life. Total colectomy and ileorectal anastomosis is a well-accepted prophylactic technique in another dominantly inherited syndrome of colorectal cancer predisposition, familial adenomatous polyposis (FAP).[25] However, FAP patients are typically in their late teens or early twenties at surgery, which is significantly younger than patients with HNPCC. The older HNPCC patients may not adapt as well to an ileorectal anastomosis and may be troubled by diarrhea and incontinence. Some of these concerns have been alleviated by a small study looking at function and quality of life,[26] but medically unfit patients who cannot tolerate an extended operation, patients with renal failure who need more absorptive capacity, and patients with poor sphincter function in which more liquid stool would worsen quality of life, are better served by a segmental colectomy. Therefore, although total colectomy reduces metachronous cancer risk, other factors such as quality of life and medical comorbidities should be considered for each individual patient.

One potential criticism of this study is the use of the clinical definition of HNPCC via Amsterdam criteria rather than genetic confirmation of a germline mutation in one of the mismatch repair genes responsible for Lynch syndrome. Because this was a retrospective study, the majority of these patients was treated in an era before the widespread availability of genetic counseling or testing. Beginning in the last few years, all patients are offered genetic testing so that we may better characterize risk for the patient and his or her family members. However, physicians must be prepared to manage families without the assistance of genetic information, as some people still refuse to undergo testing. Even for those who undergo testing, not all mutations, insertions, or deletions are found. Tumor testing by microsatellite instability analysis and immunohistochemistry substitute for germline mutation testing. If a cancer in a

patient belonging to an HNPCC family is microsatellite unstable, or shows lack of expression of a mismatch repair protein, that is good evidence for Lynch syndrome and a strong indication for aggressive resection. Sometimes these tests are done preresection on endoscopic biopsies, allowing the results to guide the definitive procedure. If microsatellite instability analysis and immunohistochemistry are not available, the Amsterdam criteria are all that clinicians can use to make surveillance or treatment decisions. The criteria do indicate a dominant inheritance, and as we have shown, convey high levels of risk for metachronous neoplasms. If all patients were genetically tested, the levels of risk would likely be higher. However, in the absence of genetic testing, we propose treating patients with colorectal cancer in families meeting Amsterdam criteria aggressively with total instead of segmental colectomy. In the absence of genetic testing it is also possible that the families of some of these patients have attenuated polyposis, either due to *APC* or *hMUTYH* mutations. Some may also have hyperplastic polyposis, the genotype of which is unknown. Differentiating syndromes is important in the context of the family, and when screening individuals for extracolonic manifestations. The potential genetic diversity does not, however, influence our conclusions about surgical choices for patients in Amsterdam positive families.

In summary, HNPCC patients with colon cancer are a high-risk group with an unstable colorectal epithelium. The transition from normal mucosa to cancer may occur in less than a year. Whether patients undergo a total or a segmental colectomy, residual colon, and rectum must be evaluated yearly. Total colectomy and ileorectal anastomosis reduces the risk of a second cancer by removing more at-risk mucosa.

ACKNOWLEDGMENTS

The authors thank Lori Arroyo, Susan Fay, Janet Shenal, Kathy Toderick, and the David B. Jagelman Inherited Colorectal Cancer Registries for recording and collection of data.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225–249.
2. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer*. 1999;81:214–218.
3. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA*. 2005;293:1979–1985.
4. Fitzgibbons RJ Jr, Lynch HT, Stanislav GV, et al. Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). *Ann Surg*. 1987;206:289–295.
5. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. *Dis Colon Rectum*. 2002;45:1588–1594.
6. Vasen HF, Mecklin JP, Khan PM, et al. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum*. 1991;34:424–425.
7. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology*. 1999;116:1453–1456.
8. Church J, Simmang C. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). *Dis Colon Rectum*. 2003;46:1001–1012.
9. Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet*. 2007;44:353–362.
10. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med*. 2003;348:919–932.
11. Church JM. Prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer. *Ann Med*. 1996;28:479–482.
12. Natarajan N, Watson P, Silva-Lopez E, et al. Comparison of extended colectomy and limited resection in patients with Lynch syndrome. *Dis Colon Rectum*. 2010;53:77–82.
13. Guillem JG, Wood WC, Moley JF, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. *Ann Surg Oncol*. 2006;13:1296–1321.
14. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118:829–834.
15. Vasen HF, Taal BG, Nagengast FM, et al. Hereditary nonpolyposis colorectal cancer: results of long-term surveillance in 50 families. *Eur J Cancer*. 1995;31A:1145–1148.
16. Lindgren G, Liljegren A, Jaramillo E, et al. Adenoma prevalence and cancer risk in familial non-polyposis colorectal cancer. *Gut*. 2002;50:228–234.
17. Rijcken FE, Hollema H, Kleibeuker JH, et al. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. *Gut*. 2002;50:382–386.
18. Rijcken FE, Koornstra JJ, van der Sluis T, et al. Early carcinogenic events in HNPCC adenomas: differences with sporadic adenomas. *Dig Dis Sci*. 2008;53:1660–1668.
19. Stoffel EM, Turgeon DK, Stockwell DH, et al. Missed adenomas during colonoscopic surveillance in individuals with Lynch Syndrome (hereditary nonpolyposis colorectal cancer). *Cancer Prev Res*. 2008;1:470–475.
20. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology*. 2007;50:113–130.
21. Jarrar AM, Church JM, Fay S, et al. Is the phenotype mixed or mistaken? Hereditary nonpolyposis colorectal cancer and hyperplastic polyposis syndrome. *Dis Colon Rectum*. 2009;52:1949–1955.
22. Liljegren A, Barker G, Elliott F, et al. Prevalence of adenomas and hyperplastic polyps in mismatch repair mutation carriers among CAPP2 participants: report by the colorectal adenoma/carcinoma prevention programme 2. *J Clin Oncol*. 2008;26:3434–3439.
23. Van Dalen R, Church J, McGannon E, et al. Patterns of surgery in patients belonging to Amsterdam-positive families. *Dis Colon Rectum*. 2003;46:617–620.
24. Rodriguez-Bigas MA, Vasen HF, Pekka-Mecklin J, et al; International Collaborative Group on HNPCC. Rectal cancer risk in hereditary nonpolyposis colorectal cancer after abdominal colectomy. *Ann Surg*. 1997;225:202–207.
25. Church JM, Fazio VW, Lavery IC, et al. Quality of life after prophylactic colectomy and ileorectal anastomosis in patients with familial adenomatous polyposis. *Dis Colon Rectum*. 1996;39:1404–1408.
26. Lynch AC, Church JM, Lavery IC. Quality of life following partial or total colectomy: relevance to hereditary non-polyposis colorectal cancer. *Dis Colon Rectum*. 2003;46:55.

Discussions

DR. ROBERT MADOFF (MINNEAPOLIS, MN): There has been much discussion about Lynch syndrome (hereditary nonpolyposis colorectal cancer), but there are very few comparative studies looking at surgical strategies.

Your median interval for surveillance colonoscopy is 2 years, but there is actually quite a broad range in your paper. Was there a difference in the screening interval between those who went on to develop cancers or advanced polyps and those that did not? And, if so, is strict surveillance colonoscopy a viable strategy for cancer prevention in Lynch patients?

Second, you make a global recommendation for total abdominal colectomy, but you could make an argument that older patients have fewer years at risk and are more likely to experience poor functional outcomes following the more aggressive operation. Is this really an one-size-operation-fits-all, or should we nuance our approach?

My third question is about using the Amsterdam criteria. As you know, these were designed to be very specific but not terribly sensitive. In the clinical setting, we often see young patients with small kindreds with poor or unreliable family histories. Should we just look at immunohistochemistry of the tumors before we operate on them and not worry so much about Amsterdam criteria?

My fourth question was not addressed by your data, but I think it is an important clinical consideration. What do you do about a patient who presents with an index cancer that is a rectal cancer? Should he or she receive a low anterior resection, proctocolectomy, or an ileoanal reservoir?

Finally, you point out that there is an 80% lifetime risk of developing colorectal cancer in Lynch syndrome, which is not all that different from what we see in FAP. You also show, almost irrespective of surgery, that there is still a substantial risk of developing another cancer later.

No one I know really advocates for proctocolectomy with ileoanal reservoir for Lynch syndrome, but I think your study begs the question, is that an appropriate operation? To whom should we offer it?

Dr. Jose Guillem (New York, NY): I was intrigued with your numbers of 20 or so percent incidence of the metachronous cancers in this patient population, and it reminded me of the work of Henry Lynch and Patrice Watson that showed years ago, in perhaps a better genetically defined population with large kindreds, that their metachronous rate at 10 years was on the order of 40%.

Is your incidence of 25% due to the fact that you are incorporating Amsterdam 1 and 2 into this Amsterdam life group that you have included as your third group?

Second, can we rely on the Amsterdam criteria. It is a quick and readily available office clinical diagnosis that helps identify an individual at risk for metachronous cancers, but I would like to hear your thoughts in terms of where you think the future lies with the ability to perform rapid, preoperative testing. Do you think that individuals with a strong family history that meets an Amsterdam criteria plus a mutation will be at a higher risk, not only of a colon cancer, but perhaps of endometrial cancers. We may be able to plan an operation that will include not only prophylactic colectomy but perhaps a prophylactic hysterectomy.

Dr. Michael Stamos (Orange, CA): Were all patients in your registry enrolled or followed from the time of their index operation, or were some of these people put in your registry at the time of their second operation, which may have occurred at your location? It would seem that if this is so, it would bias the data.

Secondly, did the age at the time of the index cancer diagnosis impact the outcome or the timing of the metachronous lesion?

Third, this data are quite compelling. Would it change your clinical approach to a patient who comes to you, after having a segmental colectomy, in terms of their risk, and would you consider a prophylactic completion colectomy?

Dr. Merril T. Dayton (Buffalo, NY): For years, the teaching was that these lesions tend to be right-sided, you perform a right colectomy, and provide surveillance. I think your paper really challenges that conventional thinking.

Having said that, 27% of the patients in this series who received a segmental colectomy went on to develop another cancer, which means that 75% did not develop another cancer. Would you offer your patients their choice regarding total colectomy versus surveillance after informing them of the risk and telling them about the change in lifestyle; there are a fair number of patients who will not develop another cancer. Those numbers are significant enough that I would, at least, discuss it with my patients and give them a choice in the matter. Our patients tend to do what we recommend, but if you discuss those incidences, some of them might elect surveillance, and perhaps a better quality of life.

Dr. Robert Fitzgibbons (Omaha, NE): About 25 years ago, I had the privilege of presenting Dr. Lynch's original work to this society, in which we recommended subtotal colectomy and ileorectal anastomosis. At that time, we were varying the length of colon removed based on a patient's risk factors for not tolerating the operation. For example, older patients would get a much longer rectal and sigmoid remnant than a pure rectal anastomosis. Does this still apply?

Dr. Matthew Kalady (Cleveland, OH): In answer to Dr. Madoff's first question, did the difference in the intervals between surveillance colonoscopies affect the rate of the cancers found, I think it makes logical sense that the longer you wait, the higher the risk of actually developing or finding a cancer will be.

The natural history will always be from normal mucosa, to an adenoma, to cancer, and whether you intervene by doing surveillance more frequently, then you will either see nothing on those surveillance exams or remove polyps before they become cancers. I cannot comment exactly whether a shorter interval would prevent cancer, but it would make sense. This was a retrospective and historical study, and the surveillance interval actually reflects more the variability of the practice over time, as well as the practice and the knowledge base of various physicians taking care of these patients, both within the Cleveland Clinic and in other institutions.

We do try to adhere to a strict prospective surveillance strategy, which leads me to the next question, is segmental colectomy with a strict surveillance strategy a viable strategy to prevent cancer? I think that is, and it needs to be studied in a more systematic way. A study conducted by our group published about 10 years ago looked at differences between patients who were treated and followed at the Cleveland Clinic versus patients who were treated elsewhere. Of 17 patients who received a segmental colectomy with a strict surveillance program, only 1 of them developed a colon cancer, as opposed to about a third of 53 patients who were followed elsewhere. Thus, I think, with the appropriate patients and the appropriate follow-up, this could be a reasonable strategy.

Several members raised the question, is total colectomy appropriate for all patients? Each case is patient specific. I do offer patients choices. I think my role and the role of all surgeons is to give patients the options and basically let them make informed decisions. Some patients will do whatever you say and other patients will do as they choose. I think, it is reasonable to explain the risks and allow for a guided choice.

Age and patient health does affect our choice of operation. Elderly patients, as was pointed out, may have fewer remaining years or issues with incontinence, and may be better served with segmental colectomy and close surveillance to preserve function. Other people with significant comorbidities may fare better with a segmental colectomy. For example, people suffering from renal failure who cannot cope with losing absorptive colon capacity may be better served by segmental colectomy as well.

Following up with Dr. Madoff, the Amsterdam criteria are clinical definitions, but why do we not just take everybody, get their tissue, and use immunohistochemistry or microsatellite status to say that these people are the ones at risk instead of using family criteria? That would work in an ideal world, but unfortunately it is not always practical. Not everyone in the country is knowledgeable about Lynch syndrome, nor do all hospitals have the ability to run those tests. Also, not everyone has access to genetic counselors to counsel patients before ordering genetic testing. It is also very important to know what to do with that information. Therefore, the Amsterdam criteria are a very good surrogate in practice in the real world.

That being said, even if a patient with cancer does not specifically meet Amsterdam criteria, but their history is suspicious, we refer them to genetic counseling at our institution and order tests

before the operation so that we can plan and give them informed consent as to what we want to do.

In the future, there will likely be rapid, readily available testing, which will lead to a more defined group; more specific than just Amsterdam criteria. There will be a much more personalized delivery of care based on the genetic mutation they possess.

In terms of what we do with the rectal cancer patients, again, it comes up to the point of individualized care. There is very little data on the natural history of this and one study reports a 12% risk of developing colon cancer after proctectomy. Follow-up and the numbers are limited. With longer follow-up and as people get older, we would see a number closer to the 80% that is given for colon cancer in Lynch syndrome.

The consequences of a total proctocolectomy are much different than just a proctectomy with colorectal or coloanal anastomosis. People can obtain very reasonable function with an ileal J pouch, but it is different than an ileorectal anastomosis. You will experience more frequent bowel movements and there are more complications associated with it. That option should not be taken lightly, but can be considered.

Related to that point, there is a question asking whether we should just offer everybody a pouch? If we offer it for FAP, why not offer it for HNPCC? The difference is that the polyp burden in FAP is much harder to control. With HNPCC, as the name implies, it is a nonpolyposis syndrome, so you might develop few adenomas that can be controlled by good colonoscopy and surveillance. Whereas with FAP, the polyps are more numerous and diffuse throughout the entire colon. With good surveillance in hereditary nonpolyposis colorectal cancer, you can decrease the cancer risk and delay the need for colectomy.

To answer Dr. Guillem on the variability in the rate of metachronous cancer formation (40% in some of the previous groups as opposed to 20% in our study) I think that the decrease in our study is somewhat related to a more aggressive screening strategy. As we become more familiar with the disease, and we screen more aggressively and we remove these polyps and high risk adenomas before they become cancers.

So, when you actually add the high risk adenoma group and the cancer group, that number comes up closer to around 40% in our study, similar to what we saw in some of the previous literature.

For Dr. Stamos, these patients were enrolled at various times. Some of them were treated at other places and then referred to us. Some of the patients came to us after developing the second cancer, and some people were under surveillance at other places and then came to our registry. There is variability, which could create some bias in the data.

Should we offer prophylactic completion colectomy for someone who is referred after segmental colectomy for an index cancer? No, but to reiterate what we already said, it is important to realize that these patients carry a real risk of developing a second cancer and a strict surveillance program will reduce much of that risk. It is not necessary to offer a prophylactic completion colectomy in that setting unless for some reason the patient cannot undergo appropriate surveillance.

Lastly, to Dr. Fitzgibbons, regarding one of the technical points, an ileorectal anastomosis is very similar to an ileosigmoid anastomosis in terms of the surgery and follow-up. The difference is that leaving more sigmoid colon, even 6 inches to a foot will preserve a little more absorptive capacity and potentially provide better function, without making surveillance any more difficult. Although you leave behind more at-risk colon, the surveillance is still easily carried out in the office as an outpatient with just a flexible sigmoidoscopy, which can be done without bowel prep and without any anesthesia. Surveying a rectosigmoid region as well as the rectum really does not make much of a difference.